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Original article

Insulin Sensitizing and Antiatherogenic Role of Adiponectin: A Cross Sectional Study among the Healthy Subjects in Kerala

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Abstract

Background of the study and objectives: Adiponectin, the most abundantly secreted adipokine plays a central role in energy homeostasis. Different studies have reported the protective role of adiponectin in obesity related complications such as insulin resistance, hypertension, dyslipidemia, atherosclerosis etc. Since not much studies were conducted to analyze the role of adiponectin in the metabolic homeostasis among the healthy population in Kerala, we designed this study. ***Materials and methods:*** This study included 170 healthy subjects of both gender in the age group of 20-60 years. Anthropometric measurements and blood pressure were recorded. BMI, WHR and BF% were calculated. Fasting blood sample was used to measure glucose, lipid profile, insulin and adiponectin. HOMA-IR, HOMA-β and QUICKI were calculated. Data was analyzed by student's 't' test and pearson's correlation analysis. $p < 0.05$ was considered statistically significant. ***Results:*** Serum adiponectin showed a negative correlation with BMI (r=-0.583) and body fat percentage (r=-0.369). An inverse significant correlation of adiponectin with serum triglycerides (p=0.01), fasting glucose (p=0.01) and HOMA-IR (p=0.001) was observed. But insulin sensitivity (QUICKI) (p=0.001) and serum HDL-cholesterol (p=0.01) showed a significant positive correlation with adiponectin. Analysis of the study subjects based on BMI showed a significant decrease in serum adiponectin (p=0.001) among obese group in comparison with normal weight subjects. Hypoadiponectinemia among obese subjects was also found to be associated with insulin resistance and decreased insulin sensitivity expressed as QUICKI. ***Conclusion:*** Serum adiponectin showed a positive correlation with insulin sensitivity and HDL-cholesterol. Adiponectin retains a significant role as a mediator of insulin resistance and atherosclerosis.

Keywords: ***Adiponectin, insulin resistance, HDL-cholesterol, Obesity, Kerala***

Introduction

Adiponectin, a 30kD cytokine peptide hormone with 244 amino acids mainly synthesized and secreted by adipocytes. It is the most abundantly secreted adipokine constituting 0.01% of total plasma proteins which is about thousand times that of other major adipokines such as leptin and ghrelin [1]. Serum adiponectin levels are found to be inversely associated with measures of obesity which forms the major health issues strongly increasing the risk of many metabolic complications with increased morbidity and mortality such as metabolic syndrome, cardiovascular diseases, respiratory disorders, diabetes, cancer etc.[2,3]. Insulin resistance is a key feature of the metabolic complications developed due to increased body fat. While most adipokines are proinflammatory in action, adiponectin exhibits anti-inflammatory, anti-atherogenic, antioxidative as well as insulin sensitizing properties [4-6] which focus the critical role of adiponectin in the maintenance of metabolic homeostasis [7].

In contrast to other adipokines, low circulating levels of adiponectin are reported to be a strong risk factor for the development of insulin resistance which contribute to diabetes mellitus, metabolic syndrome, coronary artery diseases etc.[8,9]. Various studies have been conducted to analyse the anti-inflammatory and anti- atherogenic role of adiponectin as well as the role in energy homeostasis and metabolism of carbohydrates and lipids. The inverse relationship between serum adiponectin and insulin resistance in several pathological conditions with high cardiovascular risk such as obesity, diabetes, metabolic syndrome etc. has been established [10,11].

Adiponectin circulates in plasma as three different multimeric complexes with different molecular weight which differ in the biological functions [12]. The high molecular weight polymeric form was identified as the biologically active form of this adipokine [13]. Adiponectin exerts its physiological functions by binding with two receptors, AdipoR1 and AdipoR2. AdipoR2 has been found to be expressed mainly in liver while AdipoR1 present in almost all tissues [14]. Studies reported that in obesity linked insulin resistance, both adiponectin and adiponectin receptors are down regulated [15,16]. Due to the unique body composition and structure characterized by increased fat accumulation even at low BMIs, Indians have an increased incidence of metabolic complication diabetes even at normal BMI but with increased waist to hip ratio. This factor makes the population highly predisposed to metabolic syndrome. The present study was undertaken to analyse the role of adiponectin in predicting the incidence of insulin resistance and thus diabetes and metabolic syndrome among the healthy adult population. Since most of the studies designed to elucidate the role of adiponectin in metabolic complications have been conducted in animal models as well as humans with metabolic disorders, we designed this cross-sectional study among the healthy subjects.

Study subjects and Methods

This observational, cross -sectional study was jointly conducted at Govt. Medical College, Thiruvananthapuram and Sree Gokulam Medical college and Research Foundation, Thiruvananthapuram, Kerala, India after obtaining the approval from Human Ethics Committee from both Institutions. One hundred and seventy (87 men and 83 women) healthy volunteers aged between 20-60years were recruited to this study. Subjects with a history of drug intake affecting the study variables and those with any of the endocrine disorders were excluded from the study. Pregnant and postpartum women and those taking oral contraceptive pills were excluded.

A detailed informed consent was obtained from each subject. All participants answered a life style questionnaire to record demographic and socio economic details, life style habits, detailed clinical history and the data were confidential. Anthropometric measurements and blood pressure were recorded. Body Mass Index (BMI), Body fat percentage (BF%) and waist to hip ratio (WHR) were calculated using anthropometric measurements. Fasting blood sample was used to measure the biochemical parameters. Blood glucose and lipid profile was done in 'Siemens Dimension' fully autoanalyzer using Flex reagent cartridges. Serum adiponectin (Bio Vendor Cat. No. RD195023100) (17) and insulin (DRG Cat No: EIA 2935) [18] were measured by ELISA sandwich method according to the manufacturer's instructions.

Markers of insulin resistance such as Homeostasis model assessment of insulin resistance HOMA-IR [19], Homeostasis model assessment of insulin secretion by beta cells of pancreas (HOMA-β) [19] and Insulin sensitivity expressed as Quick Insulin sensitivity Check Index (QUICKI) [20] were calculated as previously defined from fasting glucose and insulin values using standard equations. Data was presented as mean±SEM and were analysed using Statistical Package for Social Sciences (SPSS) for Windows version 17.0 (SPSS Inc, Chicago, IL, USA). Correlation of serum adiponectin with markers of insulin resistance and lipoproteins were analyzed by Pearson's correlation. To analyze the role of adiponectin in the development of metabolic complications relating insulin resistance, the study population was grouped based on BMI and analyzed the data by unpaired Student's 't' test. The statistical significance was defined by $p<0.05$.

Results

Serum adiponectin showed a statistically significant ($p<0.001$) negative correlation with BMI (r= -0.583), waist circumference (r= -0.498), hip circumference (r = -0.470), WHR (r = -0.3) and body fat (r= -0.337) and serum triglycerides (r= -0.189, $p<0.01$) while no significant correlation was observed with serum total cholesterol and LDL-cholesterol levels (**Table1**). But statistically significant positive correlation was observed between adiponectin and HDL-cholesterol (r= 0.206, $p<0.01$) indicating the anti- atherogenic role of adiponectin. A significant negative correlation of serum adiponectin observed with serum insulin and insulin resistance expressed as HOMA-IR ($p=0.001$) (**Fig1**), while a significant positive correlation observed with insulin sensitivity expressed as QUICKI (r= 0.417, $p=0.001$) (**Fig2**).No statistically significant correlation was observed between serum adiponectin and the rate of synthesis of insulin expressed as HOMA- β (**Table1**).

Table 1: Correlation of serum adiponectin with study variables

Study variable	r	p value
Weight (Kg)	-0.508	0.001
Height (cm)	0.047	NS
BMI (Kg/ m^2)	-0.583	0.001
Waist circumference (cm)	-0.498	0.001
Hip circumference (cm)	-0.470	0.001
Waist to Hip Ratio (WHR)	-0.297	0.001
Body Fat (%)	-0.337	0.001
Fasting plasma Glucose (mg/dl)	-0.180	0.01
Total cholesterol (mg/dl)	-0.043	NS
Triglycerides (mg/dl)	-0.189	0.01
HDL-Cholesterol (mg/dl)	0.206	0.01
LDL-Cholesterol (mg/dl)	-0.030	NS
Serum Insulin (µIU/ml)	-0.392	0.001

HOMA -IR	-0.369	0.001
HOMA -β	-0.073	0.05
QUICKI	0.417	0.001

Data analyzed by pearson's correlation. p< 0.05 considered statistically significant. NS-Not Significant

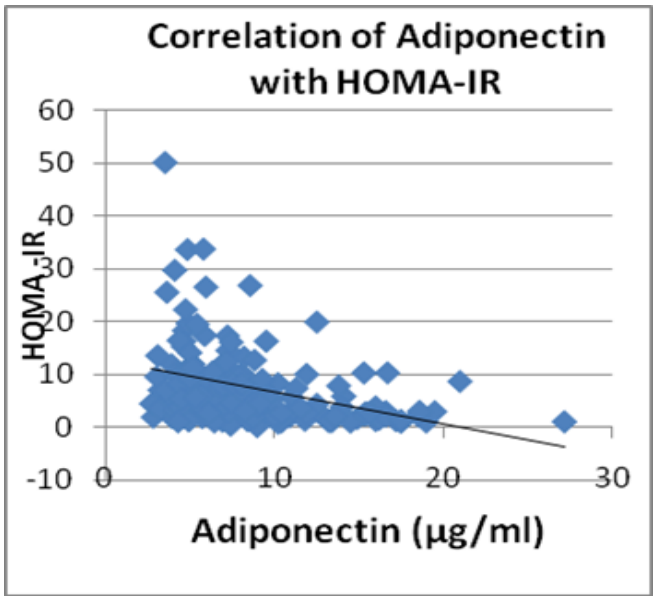

Fig1: Correlation of adiponectin with HOMA-IR

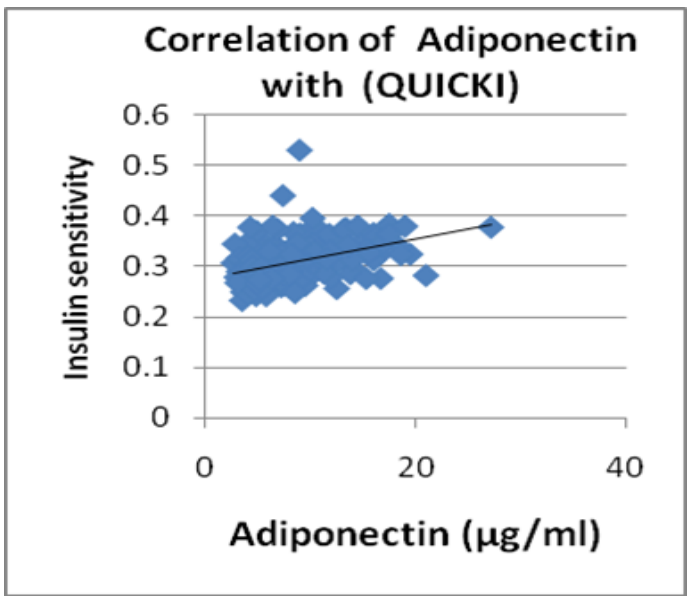

Fig2: Correlation of adiponectin with Insulin sensitivity

In order to analyze the role of adiponectin in the regulation of body fat mass and metabolic homeostsis we grouped the study subjects in to two (case and control) based on BMI with a cutoff point of 25 kg/m^2. The mean BMI of case (obese group) was29.3 kg/m^2 and that of control group was 21.5 kg/m^2 (**Table 2**). There was no statistically significant difference in age between the two groups. Waist circumference and body fat percentage showed a statistically significant difference (p=0.001) between the two groups. The serum adiponectin level (µg/ml) was found to be decreased significantly (p=0.001) in obese group (6.28±2.05) compared to control group (11.95±4.65).

Table 2: Adiposity measures and serum Adiponectin based on BMI

Study variable	Control (n=71)	Obese (n=99)	p value
Age (yrs)	37 ± 11.8	42.4 ± 10.8	NS
Weight (kg)	57.5 ± 9.6	76.1 ± 10.6	0.001
Height(cm)	163.4 ± 9.4	161.1 ± 8.2	NS
BMI (kg/m^2)	21.5 ± 2.4	29.3 ±3.9	0.001
Waist circumference(cm)	82.4 ± 8.7	100.45 ± 9.1	0.001
Hip circumference(cm)	90.3 ± 8.0	105.8 ± 7.9	0.001
WHR	0.91 ± 0.04	0.95 ± 0.05	0.001
Body Fat (%)	25.6 ± 7.0	37.4 ± 8.9	0.001
Serum adiponectin (µg/ml)	11.95 ± 4.65	6.28 ± 2.05	0.001

Data expressed as mean ±SEM analysed by student's 't' test. P<0.05 considered significant

Serum insulin level (µIU/ml) was found to be elevated significantly among obese subjects (36.79±2.3, mean±SEM) compared with control (16.6±2.0, mean±SEM) (p=0.001) (**Fig 3**). No statistically significant difference observed in fasting plasma glucose between the groups. There was no statistically significant difference in the rate of insulin synthesis expressed as HOMA-β between the two groups (**Fig 4**). In terms of BMI, this study showed a statistically significant increase in insulin resistance (HOMA-IR) (**Fig 5**) with a significant decrease in insulin sensitivity (QUICKI) (**Fig 6**) in obese group (BMI>=25kg/m^2) compared to control group (BMI<=24.9kg/m^2) Insulin resistance expressed as HOMA-IR was strongly associated with obese group (9.86±0.79) in comparison with control group (3.8 ± 0.45). Insulin sensitivity expressed as QUICKI showed a significant decrease in obese group in comparison with control group (p=0.001).

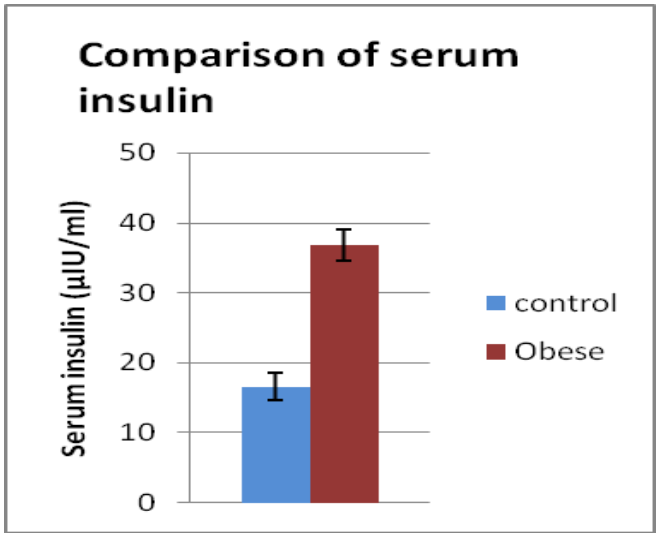

Fig3: Comparison of serum insulin based on BMI

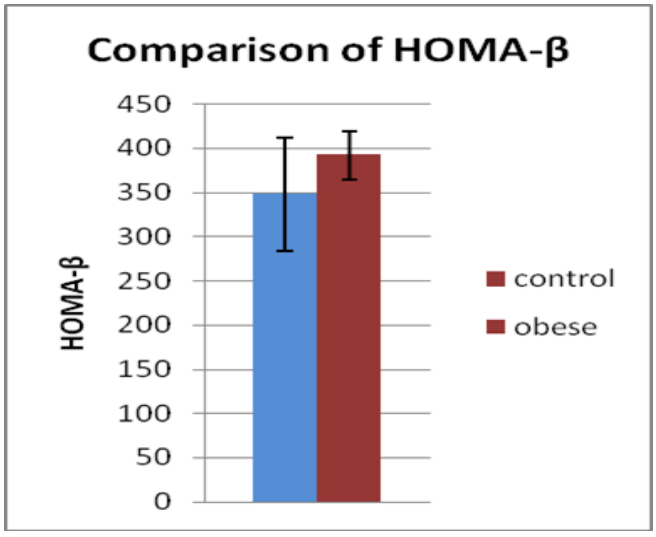

Fig4: Comparison of rate of insulin synthesis based on BMI

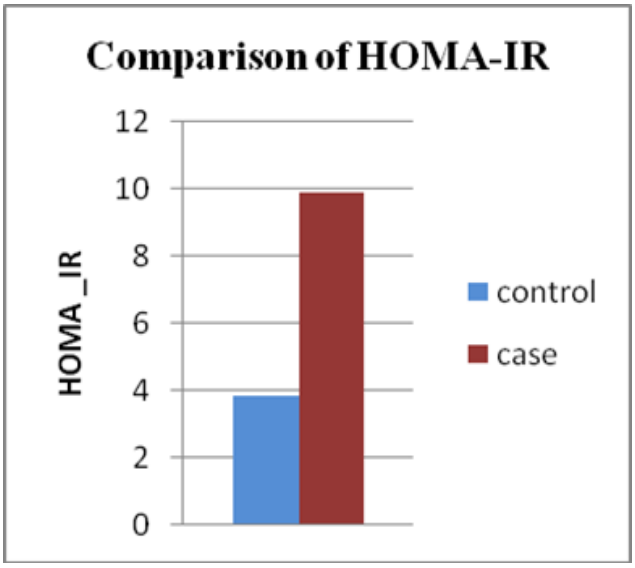

Fig5: Comparison of insulin resistance based on BMI

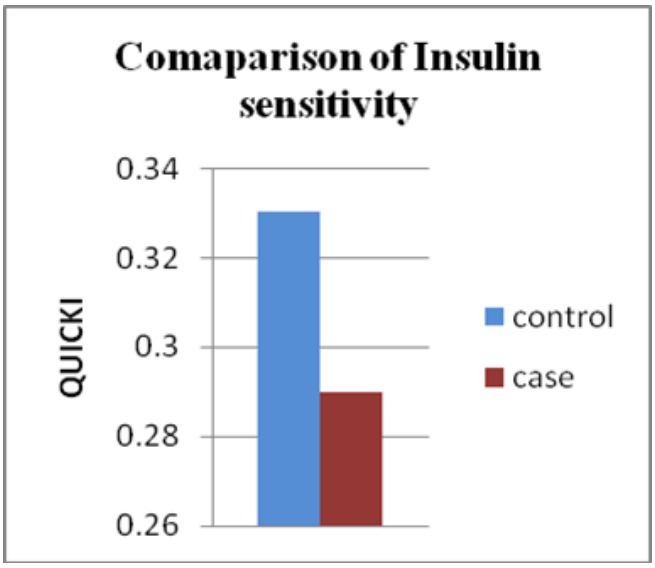

Fig6: Comparison of insulin sensitivity based on BMI

The difference observed in the lipids and lipoprotein levels between obese and control groups was not statistically significant. (**Fig 7**). Even though there was a decrease in HDL-cholesterol in obese group (48.25±1.2) in comparison with control group (52.95± 1.6), the difference was not statistically significant.

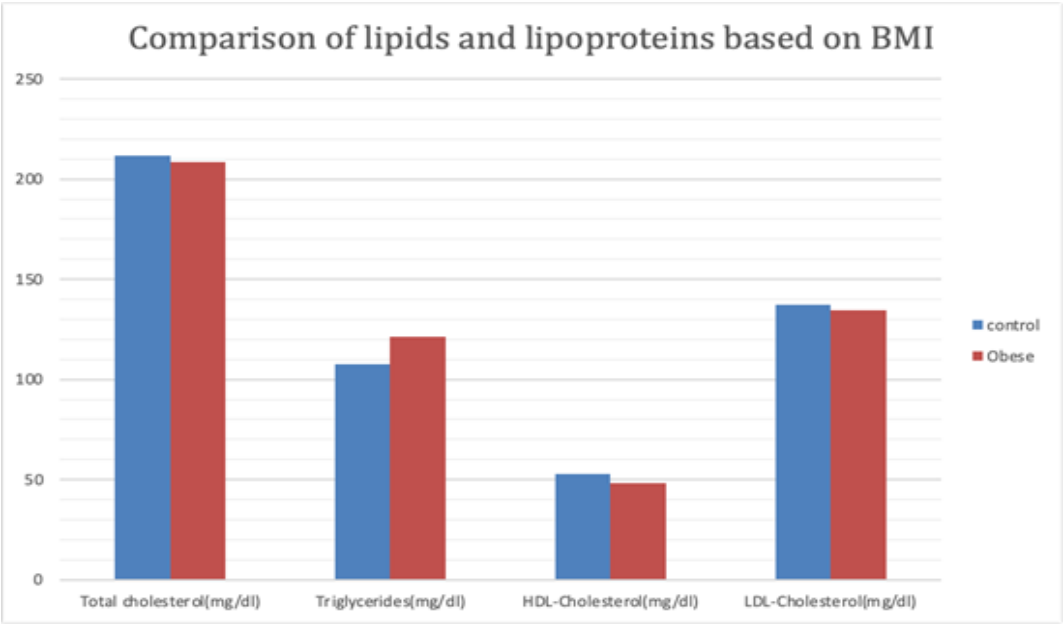

Fig7: Comparison of lipids and lipoproteins based on BMI

Discussion

Adiponectin, the recently discovered adipocyte specific collagen-like protein is pleotropic in action targeting the liver, heart, pancreas, kidney, skeletal muscle and many other tissues to regulate insulin sensitivity, energy balance and cellular metabolism via receptor dependent mechanisms [8,10,13]. Different studies reported the central role of hypoadiponectinemia in obesity related diseases mediated by insulin resistance. The present study conducted among healthy subjects observed a negative correlation of adiponectin with BMI, waist circumference, WHR and total body fat and a positive correlation with HDL cholesterol as well as insulin sensitivity (QUICKI). This is in agreement with the study of Amit et al. in north Indian population [21]. During the correlation analysis of adiponectin with study variables, a strong negative correlation was observed with waist circumference (r= -0.498) which is a better index of visceral obesity when compared with total body fat (r= -0.337). This is in agreement with the study of Graciela et al. [3]. Based on a study with isolated adipocytes, Fain et al. reported that there was no difference in secretion of adiponectin from visceral or subcutaneous depots [22]. According to Motoshima et al. regulation of rate of secretion of adiponectin exhibits some depots specifically [23]. This could explain the finding that even after controlling the BMI and fat mass, individuals with higher visceral fat have lower adiponectin level than those with less visceral fat.

In our study population, the plasma adiponectin levels negatively correlated with serum insulin, insulin resistance (HOMA-IR), but positively correlated with physiological estimate of insulin sensitivity (QUICKI). But there was no significant association between serum adiponectin level and the rate of synthesis of insulin expressed as HOMA-β. This is in agreement with previous studies showing the strong relationship between plasma adiponectin levels with the components of metabolic syndrome [24-26]. According to Bacha et al. adiponectin levels accounted for 73% of variance in insulin sensitivity [27].

Our study agrees previous findings that obesity is associated with low serum adiponectin concentrations [28.29]. In accordance with Katherine et al. our study showed a positive correlation with HDL-cholesterol [30]. The observations in our study also pointed to the significant role of adiponectin as a potent antiatherogenic and insulin sensitizing adipokine.

Conclusion

Serum adiponectin showed a positive correlation with insulin sensitivity and HDL-cholesterol. The decrease in serum adiponectin among obese subjects has been found to be associated with the development of insulin resistance. So hypoadiponectinemia may not be a major cause of obesity. Instead, it could be the result of obesity induced insulin resistance, due to decreased insulin sensitizing action of adiponectin.

Ethical Approval and Consent to participate

The study was approved by the Human Ethics Committee of both Institutions. A written informed consent was obtained from each participant.

Data Availability Statement

All the data used in writing the article are included in the manuscript

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article

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Authors Contributions

KTS and MKS made substantial contributions to conception and design of the study. Data collection done by MKS, LKB and VL. MKS executed the experiment. All authors participated in drafting the article and approved the content for publication.

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List of Abbreviations

BMI: Body Mass Index
WHR: Waist to Hip Ratio
BF: Body Fat
HOMA-IR: Homeostasis Model Assessment of Insulin Resistance
HOMA- β: Homeostasis Model Assessment -beta
QUICKI: Quick Insulin Sensitivity Check Index
HDL-Cholesterol: High Density Lipoprotein Cholesterol
LDL-Cholesterol: Low Density Lipoprotein Cholesterol
kD: Kilo Dalton
ELISA: Enzyme Linked Immunosorbent Assay

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